Chalder, T. & Willis, C. (in press). 'Lumping' and 'splitting' medically unexplained symptoms: Is there a role for a transdiagnostic approach? *Journal of Mental Health*

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Conflict of Interest:

Overcoming Chronic Fatigue by Mary Burgess and Trudie Chalder, Robinson Publishing Ltd.

Overcoming Chronic Fatigue in Young People: A cognitive behavioural self help guide by Katherine Rimes and Trudie Chalder, Routledge.

Coping with Chronic Fatigue: Overcoming Common problems by Trudie Chalder, Sheldon Press.

Abstract

Medically Unexplained Symptoms are highly prevalent in both primary and secondary care and are seen in all medical specialties. For example, fibromyalgia is seen in rheumatology, irritable bowel syndrome in gastro-enterology, non-cardiac chest pain in cardiology. These syndromes have been studied in isolation yet there is considerable overlap in symptoms with more than half of patients with one MUS fulfilling diagnostic criteria for one other. This suggests that MUS could be 'lumped'. However, research has observed that symptom overlap is not present between all MUS. There are differences in pathophysiology and cognitive and behavioural responses between syndromes. This has generated ongoing debate as to whether MUS should be 'lumped' or 'split'. We argue that a transdiagnostic approach that is flexible enough to treat specific responses peculiar to certain conditions could accommodate both 'lumping' and 'splitting'.

Medically unexplained syndromes (MUS) are defined as persistent bodily symptoms with functional disability but no explanatory pathology. They are highly prevalent in both primary and secondary care. In a meta-analysis of medically unexplained symptoms (not syndromes) in primary care, the percentage of patients complaining of at least one medically unexplained symptom ranged from 40.2% (95% CI 0.9–79.4%; I2 = 98%) to 49% (95% CI 18–79.8%, I2 = 98%) (Haller et al., 2015). MUS are associated with high levels of distress and do not respond easily to reassurance and simple explanation (Barsky & Borus, 1999). They are seen in all medical specialties. Fibromyalgia (FM) is frequently seen in rheumatology, irritable bowel syndrome (IBS) in gastroenterology, non-cardiac chest pain in cardiology, chronic fatigue syndrome (CFS) in infectious diseases, non-cardiac chest pain and functional palpitations in cardiology, hyperventilation syndrome in respiratory medicine, tension headache in neurology and multiple chemical sensitivity in allergy. These syndromes have mostly been studied in isolation. However, research has observed extensive symptom overlap with more than half of patients with one MUS condition fulfilling diagnostic criteria for at least one other MUS condition (Nimnuan et al., 2001). For this reason, Wessely et al. (1999) suggested advantages to redefining MUS as one syndrome. Fink and Schroder (2010) advocated a new over-arching term, "bodily distress syndrome", to encompass all the different MUS. They submit that there is now substantial evidence that MUS conditions are not clearly distinct disease entities but rather a common phenomenon with different subtypes. They describe similarities in diagnostic criteria, aetiology, pathophysiological, neurobiology, psychological mechanisms, patient characteristics and treatment response. Some years earlier Yunus (2007) had suggested the generic term "central sensitivity syndrome" which suggests that the common mechanism underlying various MUS is central sensitisation which is the hyper-excitement of neurons in the central nervous system.

However, this "lumping" hypothesis triggered much debate due to criticisms that overlap is not present between all the MUS. For instance, there is little symptomatic overlap between IBS and FM. Furthermore, the pathophysiology is not consistent across syndromes in that there is hyperactivity of corticotropin-releasing hormone neurons in FM but hypoactivity in CFS (Neeck & Crofford 2000). From a cognitive behavioural perspective unhelpful beliefs and behaviours may differ markedly from one syndrome to another.

The study of MUS often attracts debate and sometimes controversy. Even the label MUS comes under fire. Persistent Physical Symptoms (PPS) is a new patient-centred term that refers to MUS. For several reasons we prefer to use the term PPS. Firstly, two surveys of different populations preferred the term. One group consisted of healthy subjects (Marks & Hunter 2014) and the other group involved patients with CFS (Picariello et al., 2015). People found the term more acceptable as it avoids mind-body dualism and has cross-cultural relevance. Secondly, it includes symptoms associated with medically diagnosed long term conditions such as diabetes, rheumatoid arthritis and multiple sclerosis which may present co-morbidly with MUS. Thirdly, it also concurs with changes in the latest edition of the Diagnostic and Statistics Manual (DSM-5). The DSM-5 has consolidated previous terms including somatization disorder, conversion disorder, hypochondriasis into a new diagnostic term, Somatic Symptom Disorder (SDD). This refers to persistent (6 months or more) and clinically significant somatic complaints accompanied by excessive and disproportionate health-related thoughts, feelings and behaviours regarding the symptoms (American Psychiatric Association, 2013). We will use the new term PPS to refer to MUS but continue to use the term MUS when referring to the work of other authors who have used this term.

The development and delivery of effective treatments for PPS is important for patients, health professionals, the wider healthcare system and the economy. There is an increasing demand

to ensure that this is achieved efficiently in an 'over-stretched' healthcare system. Prevalence of MUS in secondary care is approximately 50% and healthcare costs are twice those of other patients (Barsky et al. 2005). Initiatives to meet this demand are being commissioned and developed. The Improving Access to Psychological Therapies (IAPT) programme is expanding to treat PPS and long term conditions (LTC's) to increase access in primary care (McCrae et al 2015).

Cognitive Behavioural Therapy (CBT) for PPS has traditionally focussed on developing specific treatment programmes for conditions such as Chronic Fatigue Syndrome (CFS) and Irritable Bowel Syndrome (IBS). This approach is supported by a good evidence base. CBT has demonstrated both short and long term efficacy with small effect sizes for MUS (Van Dessel, et al., 2014) yet larger treatment effects are seen in specific syndromes such as CFS (White et al., 2011) and IBS (Altayer et al., 2011).

Given the overlap between syndromes and the fact that the stability of diagnoses within individuals is low it is highly probable that a number of core transdiagnostic aetiological factors underlie the disorders and that common processes perpetuate the symptoms and disability. We and others have identified cognitive and behavioural responses to symptoms that are common across MUS conditions. For example such cognitive and behavioural responses include avoidance of activity and focussing on symptoms (Deary et al., 2007; Spence & Moss-Morris, 2007). In both IBS and CFS participants hold significantly more beliefs about the unacceptability of emotions compared to healthy controls (Bowers & Wroe 2015; Rimes & Chalder 2010).

The transdiagnostic approach while addressing common processes is flexible enough to address issues specific to the disorder. For example, research has identified different aetiological pathways for the development of CFS and IBS. CFS is more likely to develop

following infection with glandular fever and IBS following campylobacter infection. Depression has been found to be a greater risk factor for CFS yet stress, anxiety and perfectionism are important predictors for IBS (Moss-Morris & Spence, 2006, 2007). While IBS and CFS share an overall transdiagnostic response of 'avoidance behaviour' they sometimes differ in the type of avoidance. IBS patients may respond to their symptoms with 'embarrassment-avoidance'. More specifically they may avoid social situations due to fear of embarrassment or fear of having an accident. However, CFS patients often report that they avoid activity or exercise in response to the symptom of fatigue due to fear of exacerbating it.

Co-morbidity of disorders and common processes are also observed in mental disorders. Transdiagnostic approaches and unified treatment protocols for mental disorders such as anxiety, depression and eating disorders have been developed to address this (Barlow et al., 2004; Fairburn et al., 2003, Kring & Sloan, 2010). They focus on identifying the core and common maladaptive temperamental, psychological, cognitive, emotional, interpersonal and behavioural processes that underlie a range of diagnostic presentations and target these in treatment (Newby et al., 2015). For example, there is evidence of mechanisms that link the process of rumination to both depression and anxiety. In depression, rumination exacerbates low mood, negative thoughts about the past, present and future and interferes with problem solving. Of course problem solving is the very thing that may lead to the behavioural resolution of problems that causes or perpetuates depression. The same mechanisms have also been found to maintain anxiety but cognition is usually focussed on future threat rather than the past (Nolen-Hoeksema & Watkins, 2011).

There is also a growing evidence base for transdiagnostic approaches for mental disorders. In their systematic review and meta-analysis, (Newby et al., 2015) concluded that transdiagnostic approaches are as effective as disorder specific treatments for treating anxiety

and may be superior for reducing depression. Similarly, Norton and Barrera (2012) observed treatment equivalence between disorder specific and transdiagnostic treatments for anxiety in a non-inferiority RCT.

We have developed a transdiagnostic cognitive behavioural approach for PPS which can also be used for long term conditions. We anticipate that the adapted transdiagnostic approach may address the need for efficiency while maintaining the efficacy of larger effects seen in specific condition treatment programmes. Our transdiagnostic approach for PPS is guided by the use of a transdiagnostic meta-model (see figure 1). It integrates predisposing and precipitating aetiological factors with perpetuating factors. As with most cognitive behavioural models, cognitive and behavioural responses are key. However, emotional responses or reactions and their corresponding physiological interactions are also considered in the maintenance of symptoms (Brown, 2004; Deary et al., 2007; Yunus 2007). Two explanatory pathways include and exclude pre-morbid physical pathology or psychopathology. Acute and recuperative stress responses are emphasised as are key physiological processes that variably interact with other factors to perpetuate symptoms. In terms of how this maps onto the treatment process an assessment of these factors and processes with each individual influences the development of a formulation. This is shared with the patient to provide explanation for their symptoms and disability and guides the selection of interventions and strategies for treatment. Table 1 summarises the transdiagnostic processes with corresponding interventions and strategies that have informed the design of the approach.

Figure 1: A transdiagnostic meta-model of Medically Unexplained Symptoms

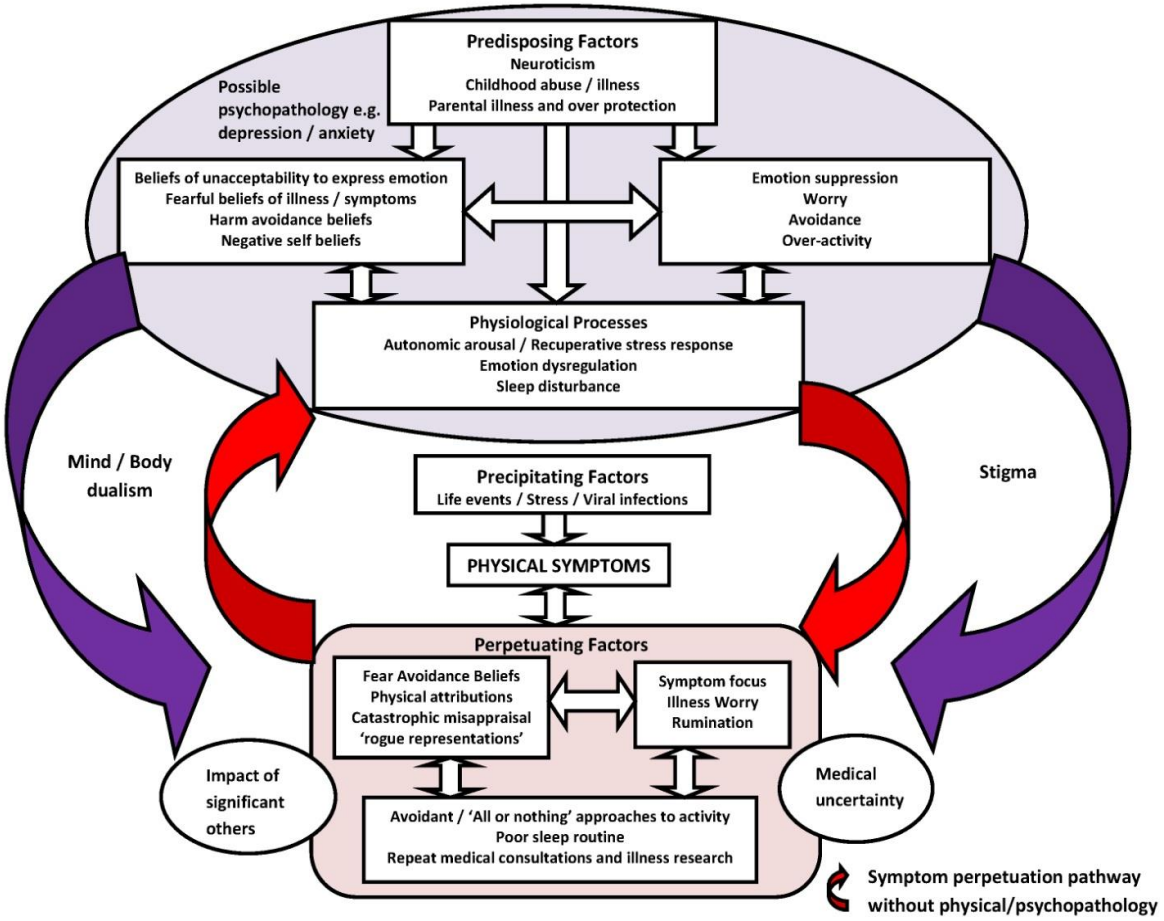

Table 1. Adapted Transdiagnostic Interventions

Process		Goal of Intervention	Strategy / Technique
Behavioural	**Activity / exercise avoidance**	To increase activity / exercise	Activity monitoring Graded exercise Behavioural activation
	All or nothing approach to activity	To Balance activity, responsibilities and relaxation	Activity monitoring and scheduling Problem solving
	Poor sleep routine	To have good quality sleep routine	Consistent wake up / sleep times Bed restriction
	Unhealthy behaviours	To maintain healthy life-style	Discussion re: balanced diet (with advice from dietician if necessary) Education re: healthy bowel habits; Discussion re: effects of alcohol Adoption of sleep routine (up time & bed and or sleep restriction) Education re: stress Graded exposure Behavioural experiments
Cognitive	**Fear Avoidance Beliefs**	To be aware of influence of thoughts Re-engage in activity /	Education re: deconditioning Behavioural experiments Socratic dialogue about

	exercise	thoughts
Physical Attributions	Understanding anatomy / physiology To broaden perspective on cause Encourage flexible attributions	Explanations Treatment as behavioural experiment
Catastrophic misappraisal /'Rogue' representations	To broaden perspective on outcomes Normalisation of symptoms	Cognitive restructuring Discussion / socratic questioning
Unhelpful thinking / worry	To facilitate objectivity / perspective on thoughts	Cognitive restructuring Mindfulness Socratic questioning Problem solving
Perfectionism	Raising self esteem without achievement focus	Behavioural experiments – Reducing standards to 80% Acceptance of self as' good enough' Compassion focussed approach
Lack of acceptance	Promote acceptance	Identification of values and development of achievable meaningful goals Discussion of adapting to a 'new healthier normal'

	Intolerance of uncertainty	Tolerance of uncertainty	Worry management techniques
	Symptom focus	To broaden focus of attention Reduce attention to body/symptoms	Discussion re: effects of attention Attention training Distraction
Emotional	**Emotion avoidance**	Acceptance of emotions Processing of emotions	Socratic dialogue about negative beliefs about emotion Mindfulness Compassion focussed approach
	Emotion dysregulation	Emotion regulation	Address trauma Discussion re: emotional processing
	Shame	Shame reduction	Cognitive restructuring 'Shame attacking' behavioural experiments Compassion focussed approach
Social	**Role of significant others**	Reduce unhelpful reinforcements Reduce reassurance seeking Facilitate a change in others behaviours	Negotiate reduction of internet searching and reassurance seeking Liaison with Healthcare Professionals Rationalise medication with agreement from physicians

It is important that the transdiagnostic approach is flexible enough to accommodate specific responses associated with different symptom clusters whilst focusing on key factors which are thought to perpetuate the problem. In order to bring some clarity to this complex issue we have organised factors and processes within a matrix framework. The Research Domain Criteria (RDoc) initiative provides a template for the development of such a framework (Morris & Cuthbert, 2012). It uses a dimensional transdiagnostic approach to capture processes (e.g. cognitive, affective, arousal) that are common across disorders. Adapting the framework we propose a two dimensional hierarchical matrix for PPS. Columns contain the superordinate processes: symptoms; physiological; emotional; cognitive, behavioural and social processes. Rows consist of both broad transdiagnostic processes as well as processes specific to conditions or symptom clusters which are potential targets (see table 2).

Ideally the matrix evolves as research identifies and develops evidence for additional factors and processes to populate the matrix cells. The strength of evidence for each factor or process could be visually represented to map strong, medium and weak evidence, creating a third dimension. In addition, moderating factors that determine the route from transdiagnostic to specific could form a network of links between factors and processes. These are described as divergent trajectories in Nolen-Hoeksema & Watkins, (2011) heuristic for developing transdiagnostic models. They describe how a transdiagnostic risk factor results in different disorders in different people or different disorders within the same person over time. Ideally these transdiagnostic mechanisms should be assessed frequently during the course of treatment so that the process of change can be assessed. In randomised controlled trials measuring both transdiagnostic and specific mediators would allow a more robust evaluation of their importance (Windgassen et al 2016).

The development of the matrix could provide a useful clinical tool to assist treatment formulations and for guiding clinicians in their treatment of PPS. It may also be used for the training and professional development of therapists.

Table 2: Proposed PPS Matrix

Condition	Symptoms	Behavioural Processes	Cognitive Processes	Physiological Processes	Emotional Processes	Social Processes
Transdiagnostic						
CFS						
IBS						
Fibromyalgia						
Non-cardiac chest pain						
Etc						

Summary and Conclusions

The high prevalence and complexity of PPS with increased access to treatment in new and developing primary care services demands a treatment approach that is effective and also 'efficient' with relative ease of dissemination across the NHS. Transdiagnostic approaches have the potential to provide effective treatment across a range of conditions that often present co-morbidly. Overlap of symptoms and co-morbidity in PPS as well as commonality in cognitive and behavioural responses suggests that a transdiagnostic approach may be suitable. We argue that a transdiagnostic approach needs to be flexible enough to accommodate specific responses peculiar to certain conditions. We are currently carrying out a randomised controlled trial (RCT) to test the efficacy of such an approach in PPS.

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